Title: Long QT Syndrome *GeneReview* – Less Commonly Mutated Genes
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Details on the less common genetic causes (i.e., each accounting for <1% of LQTS) from Table 2b. Note: Genes are ordered alphabetically.

AKAP9

Gene structure. *AKAP9* consists of 50 exons and encodes a protein of 3,907 amino acids (NM_005751.4). A shorter isoform exists.

Pathogenic variants. One pathogenic missense variant in *AKAP9* associated with LQTS has been described.

Normal gene product. The A kinase (prka) anchor protein (yotiao) 9 is involved in macromolecular complexes controlling phosphorylation of a number of proteins, including the Iks channel.

Abnormal gene product. Pathogenic loss-of-function variant resulting in an IKs channel with reduced function

ANK2

Gene structure. *ANK2* consists of 46 exons spanning approximately 350 kb; it encodes a protein of 3,957 amino acids (NM_001148.4). Alternative spliced variants exist.

Pathogenic variants. More than 20 pathogenic variants in *ANK2,* associated with LQTS, have been described.

Normal gene product. Ankyrin 2, neuronal is required for targeting and stability of Na/Ca exchanger 1, Na/K ATPase, and InsP3 receptor in cardiomyocytes.

Abnormal gene product. Pathogenic loss-of-function variant resulting in disturbed coordination of multiple functionally related ion channels and transporters

CACNA1C

Gene structure. *CACNA1C* consists of 47 exons spanning approximately 650 kb; it encodes a protein of 2,138 amino acids (NM_000719.6). Multiple alternative spliced variants exist.

Pathogenic variants. Only a few pathogenic variants in *CACNA1C* associated with long QT/Timothy syndrome have been described.

Normal gene product. The calcium channel, voltage-dependent, L type, alpha 1C subunit is the alpha-1 subunit of a cardiac voltage-dependent calcium channel .

Abnormal gene product. Pathogenic variants in exons 8 or 8A causing reduced channel inactivation, resulting in maintained depolarizing L-type calcium currents

CALM1

Gene structure. *CALM1* consists of six exons spanning approximately 11 kb; it encodes a protein of 149 amino acids (NM_006888.4).

Pathogenic variants. Only a few pathogenic variants in *CALM1* have been described.

Normal gene product. Calmodulin 1 is a calcium-modulated protein regulating L-type calcium channel function.

Abnormal gene product. Pathogenic variants in *CALM1* result in several-fold reduction in calcium-binding affinity.

CALM2

Gene structure. *CALM2* consists of six exons spanning approximately 16 kb; it encodes a protein of 149 amino acids (NM_001743.4).

Pathogenic variants. Only a few pathogenic variants in *CALM2* have been described.

Normal gene product. Calmodulin 2 is a calcium-modulated protein regulating L-type calcium channel function.

Abnormal gene product. Pathogenic variants in *CALM2* result in several-fold reduction in calcium-binding affinity.

CAV3

Gene structure. *CAV3* consists of two exons spanning approximately 12 kb; it encodes a protein of 151 amino acids (NM_033337.2).

Pathogenic variants. Five probable LQTS-causing missense variants in *CAV3* have been described.

Normal gene product. The caveolin-3 protein is the major scaffolding protein present in caveolae in the heart.

Abnormal gene product. Persistent late sodium current

KCNE1

Gene structure. *KCNE1* consists of three exons spanning approximately 40 kb, it encodes a protein of 129 amino acids (NM_000219.3).

Pathogenic variants. At least 36 pathogenic variants have been described, including pathogenic missense, nonsense, and frameshift variants.

Normal gene product. The potassium voltage-gated channel subfamily E member 1 is the beta subunit forming the slowly activating potassium delayed rectifier IKs. The two subunits encoded by *KCNE1* and *KCNQ1* coassemble to form the IKs channel.

Abnormal gene product. IKs channel with reduced function

KCNE2

Gene structure. *KCNE2* consists of three exons spanning approximately 40 kb; it encodes a protein of 123 amino acids (NM_172201.1).

Pathogenic variants. At least 20 pathogenic variants have been reported; they include missense and frameshift variants (see Molecular Genetic Pathogenesis).

Normal gene product. The potassium voltage-gated channel subfamily E member 2 is the beta subunit forming the rapidly activating potassium delayed rectifier IKr. The two subunits encoded by *KCNH2* and *KCNE2* coassemble to form the IKr channel.

Abnormal gene product. IKr channel with reduced function

KCNJ2

Gene structure. *KCNJ2* consists of two exons spanning approximately 15 kb; it encodes a protein of 428 amino acids (NM_000891.2).

Pathogenic variants. More than 70 pathogenic variants in *KCNJ2* associated with long QT/Andersen-Tawil syndrome have been described.

Normal gene product. The potassium channel, inwardly rectifying subfamily J, member 2 is an inward-rectifier type potassium channel (Kir2.1).

Abnormal gene product. Dominant-negative pathogenic variants resulting in decreased potassium currents

KCNJ5

Gene structure. *KCNJ5* consists of three exons spanning approximately 30 kb; it encodes a protein of 419 amino acids (NM_000890.3).

Pathogenic variants. Two pathogenic missense variants in *KCNJ5* associated with LQTS have been described.

Normal gene product. The potassium inwardly-rectifying channel, subfamily J, member 5 is a subunit of the cardiac inwardly rectifying potassium channel IKACh.

Abnormal gene product. Pathogenic loss-of-function variant resulting in an IKACh channel with reduced function

SCN4B

Gene structure. *SCN4B* consists of five exons spanning approximately 20 kb; it encodes a protein of 228 amino acids (NM_174934). A shorter isoform exists.

Pathogenic variants. Two pathogenic missense variants in *SCN4B* have been associated with LQTS.

Normal gene product. The sodium channel protein type IV beta subunit is a beta subunit forming the cardiac sodium channel.

Abnormal gene product. Pathogenic loss-of-function variant resulting in a cardiac sodium channel with increased persistent inward current

SNTA1

Gene structure. *SNTA1* consists of eight exons spanning approximately 35 kb; it encodes a protein of 505 amino acids (NM_003098.2).

Pathogenic variants. Three pathogenic missense variants in *SNTA1* associated with LQTS have been described.

Normal gene product. The alpha-1 syntrophin is a scaffolding protein involved in macromolecular complexes controlling the function of, among others, the cardiac sodium channel.

Abnormal gene product. Pathogenic loss-of-function variant resulting in a cardiac sodium channel with increased persistent inward current